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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/513,151 02/25/00 HEKIMI

S 979-1-017

EXAMINER

HM22/0315

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CANELLA, K
ART UNIT PAPER NUMBER

1642
DATE MAILED:

03/15/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

09/513,151

Applicant(s)

Hekimi et al

Examiner

Kar n Can lla

Group Art Unit

1642



☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 35 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) 1-20 is/are pending in the applicat

Of the above, claim(s) 7-20 is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-6 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

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DETAILED ACTION

1. Acknowledgment is made of applicants election with traverse of Group I, drawn to GRO genes and GRO-co-expressed genes. The traversal is on the grounds that the restriction is improper, that the claims of Groups II, drawn to GRO proteins and GRO co-expressed proteins, and the claims of Group IV, drawn to a method for diagnosing cancer comprising the analysis of GRO genes, should be considered with the claims of Group I because Groups II and IV both rely on the GRO gene by definition. This is not found persuasive. The protein product of Group II is structurally and functionally a distinct product from the polynucleotides of Group I, and can be made by chemical methods unrelated to the expression of the recombinant polynucleotides.

The inventions of Group I and IV are related as product and process of use, since the gro-1 wild-type gene can be used as a control sample in the method of Group IV. However, the inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the polynucleotides of group I can be used in a process to make a non-human animal expressing the gro-1 protein.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, as made of record in Paper No. 5 and recognized divergent subject matter and because the searches required for the groups are not co-extensive, restriction for examination purposes as indicated is proper. For these reasons the restriction requirement is deemed to be proper and is adhered to. The requirement is therefore made FINAL.

2. Claims 1-20 are pending. Claims 7-20, drawn to non-elected inventions are withdrawn from consideration. Claims 1-6 are examined on the merits.

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Claim Rejections - 35 USC § 101

3. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

4. Claims 1-6 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well established utility. The disclosed utilities for the gro-1 gene and related genes located in the gro-1 operon are the expression of proteins that function at the level of cellular physiology involved in developmental rate and aging in *C. Elegans*. The specification teaches that the gro-1 genes are isolated from *C. Elegans* and that worms harboring a mutation in gro-1 have a longer life and an altered cellular metabolism relative to the wild type. The specification teaches that the predicted amino acid sequence encoded by the gro-1 transcript is highly similar to dimethylallyltransferase (pg. 13, lines 20-24) found in *E. Coli* and *S. Cerevisiae*. Additionally, the specification discusses the similarity of the gro-1 gene and a human EST (Genbank Z40724). However, neither the specification nor any art of record teaches

- (a). The actual expression of hgro-1p as a protein in humans
- (b). The functioning of the hypothetical hgro-1p as a mediator of development and aging in humans, or as a mediator in any other human disease.

(A) As drawn to the expression of a gro-1 protein in humans

Although the specification teaches that a human ESTs can be used to construct a polynucleotide having similarity to the *C. Elegans* gro-1 gene, this does not represent evidence that this polynucleotide is expressed as a protein in humans. Those of skill in the art recognize that expression of mRNA does not dictate the translation of such mRNA into a polypeptide. For example, Alberts et al. (*Molecular Biology of the Cell*, 3rd edition, 1994, page 465) teach that translation of ferritin mRNA into ferritin polypeptide is blocked during periods of iron starvation. Likewise, if excess iron is available, the transferrin receptor mRNA is degraded and no transferrin receptor polypeptide is translated. Many other proteins are regulated at the translational level

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rather than the transcriptional level. For instance, Shantz and Pegg (Int J of Biochem and Cell Biol., 1999, Vol. 31, pp. 107-122) teach that ornithine decarboxylase is highly regulated in the cell at the level of translation and that translation of ornithine decarboxylase mRNA is dependent on the secondary structure of the mRNA and the availability of eIF-4E, which mediates translation initiation. McClean and Hill (Eur J of Cancer, 1993, vol. 29A, pp. 2243-2248) teach that p-glycoprotein can be overexpressed in CHO cells following exposure to radiation, without any concomitant overexpression of the p-glycoprotein mRNA. In addition, Fu et al (EMBO Journal, 1996, Vol. 15, pp. 4392-4401) teach that levels of p53 protein expression do not correlate with levels of p53 mRNA levels in blast cells taken from patients with acute myelogenous leukemia, said patients being without mutations in the p53 gene. Thus, predictability of protein translation is not necessarily contingent on mRNA expression due to the multitude of homeostatic factors affecting transcription and translation. Therefore, one of skill in the art would not be able to predict if the human polynucleotide having homology to the gro-1 gene was in fact translated into the hgro-1p protein of figures 9A and 9B. The teachings in the specification are an invitation to experiment wherein the artisan is invited to elaborate a functional use for a putative polypeptide. Because the claimed invention is not supported by a specific substantial asserted utility for the reasons set forth, credibility of any utility cannot be assessed.

(B) As drawn to the function of the hypothetical hgro-1p protein.

The specification teaches that the predicted amino acid sequence encoded by the gro-1 transcript is highly similar to dimethylallyltransferase (pg. 13, lines 20-24) which is strongly conserved in yeast and E. Coli. However the specification does not present objective evidence supporting the claim that the hypothetical hgro-1p mediates development and aging or any other disease process in humans or any other higher mammal. Although the enzyme dimethylallyltransferase is highly conserved in bacteria and lower eukaryotes, it does not necessarily follow that it is highly conserved in higher mammals. For instance, the enzyme DNA photolyase is found in bacteria, lower eukaryotes, drosophila and marsupials. However, DNA

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photolyase activity is not found in placental mammals (DNA Repair and Mutagenesis, Friedburg et al Ed., 1995, p.94, although a human mRNA having homology to drosophila photolyase has been identified (PubMed D83702). The utility of the gro-1 gene put forth in the instant specification is based on the observation that the translated amino acid sequence of the C. Elegans gro-1 gene has chemical and structural homology to a hypothetical human protein obtained by the conceptual translation of a series of overlapping human EST sequences and that both the gro-1 protein and the putative hgro-1p protein have a C2H2 zinc finger motif. However, it is clear that, although there is some amino acid identity between the gro-1 protein and the hypothetical hgro-1 protein, there are substantial dissimilarities between the two protein sequences and the effects of these dissimilarities upon protein structure and function cannot be predicted. Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine residue at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of

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aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. Clearly, the function of the hypothetical hgro-1p protein could not be predicted, based on sequence similarity with the gro-1 protein.. In addition, Bork (Genome Research, 2000,10:398-400) clearly teaches that alternative splicing might affect more than 30% of human genes and the number of known post-translational modifications of gene products is increasing constantly so that complexity at protein level is enormous. Each of these modifications may change the function of respective gene products drastically (p. 399, col 1). Clearly, given not only the teachings of Bowie et al, Lazar et al and Burgess et al but also the unknown effects of alternative splicing, post translational modification and cellular context on protein function as taught by Bork, the function of the hypothetical hgro-1p protein could not be predicted, based on sequence similarity with the gro-1 protein. The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the disclosed nucleic acids. Because the claimed invention is not supported by a specific asserted utility for the reasons set forth, credibility of any utility cannot be assessed.

5. Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Specifically, since the claimed invention is not supported by a well established utility for the reasons set forth in the rejection under 35 USC 101 above, one skilled in the art clearly would not know how to use the claimed invention.

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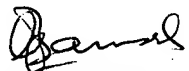
Conclusion

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella, Ph.D.

Patent Examiner, Group 1642

March 11, 2001


GEETHA P. BANSAL
PRIMARY EXAMINER